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Applicant	:	Brita Sjöblom
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Examiner	:	A. Pulliam
Art Group	:	1615

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8

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ATTENTION: **Examiner A. Pulliam**
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Declaration of Anne Mari Juppo
(Under 37 C.F.R. §1.132)

Sir:

I, Anne Mari Juppo, declare as follows:

1. I am a citizen of Finland. I graduated in 1995 from the University of Helsinki, Finland, with a doctorate in Pharmaceutical Technology.

2. The assignee of the referenced application is AstraZeneca AB. I am presently employed by AstraZeneca and my current position is Team Manager/Principal Scientist in Product Development. I have held this position since 2000. During the period 1996-2000, I was employed as a research scientist and project leader in Pharmaceutical Technology Solids and as a research scientist in Product Development.

In addition to my employment at AstraZeneca, I have been an adjunct professor since 2001 in Pharmaceutical Product Development at the University of Helsinki, Finland. My curriculum vitae is attached to this Declaration as Exhibit A.

3. I have read and understood the referenced patent application. I am familiar with the invention described and claimed therein.

4. The claimed invention is directed to a method for the preparation of homogeneous microparticles comprising a pharmaceutically active substance and a polymer. Specifically, a liquid medium having a minimum dry content of 15% by volume is atomized into droplets. The liquid medium comprises a pharmaceutically active substance, a polymer present in the amount of at least 5% by weight based upon the dry content of the liquid medium, and a liquid in which the pharmaceutically active substance and polymer are suspended, dissolved or emulsified. The droplets are frozen by a cold medium, e.g., a liquid gas. The frozen liquid of the frozen droplets are sublimated to obtain dry, homogenous microparticles.

5. The homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance. Advantageously, microparticles prepared in accordance with the claimed method have a low friability and other mechanical properties enabling them to undergo a fluidized bed coating process without disintegrating or otherwise losing their shape and structural integrity.

6. It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder. Therefore, in accordance with the claimed invention, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%.

7A. It is my understanding GB 2 329 124 to Ratwatte ("Ratwatte") has been cited against the patentability of the claimed invention.

7B. Example 1 of Ratwatte discloses a method wherein an agent composition is dispersed in a solution of a coating material in a liquid carrier material to form a dispersed mixture which is then sprayed to form droplets of the dispersed mixture. The droplets are frozen and dried to produce a plurality of coated individual particles.

7C. Example 2 of Ratwatte appears to disclose a method of preparing homogenous microparticles. However, the method and microparticles of Example 2 of Ratwatte are different from the claimed invention. In accordance with Example 2 of Ratwatte, a mixture is formed by

adding a drug to a stabilizing formulation consisting of water, a carbohydrate and a surfactant. In contrast to the claimed invention, polymer is absent from the mixture. The mixture without polymer is sprayed from a nozzle into a moving stream of air that is cooled below the freezing point of the mixture to form frozen droplets which are freeze-dried to produce particles consisting of a homogenous mixtures of the drug and stabilizing formulation. Ratwatte discloses that the particles of Example 2 can be coated in the same way as the particles of Example 1.

8A. A working example of the claimed invention is provided by Example 1. As shown in Example 2, the homogeneous particles of Example 1 are coated by a fluidized bed coating process without disintegrating or otherwise losing their shape and integrity.

8B. The following Examples 3-10 follow the preparation of microparticles in accordance with the procedure of Example 1. Only original Example 1 and Example 3 meet the requirements of the claimed invention wherein the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. In Examples 4-10, the minimum dry content and/or polymer binder content deviate from the express requirements of the claimed invention. The table provides a summary of the contents and properties of the respective particles prepared in accordance with Examples 1 and 3-10.

Example 3: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	300 g
HPMC, 6 cps	79.7 g
Tween 80 (polysorbate 80)	6 g
Purified water	827.4 g

Weight percent of dry content in suspension: 31.8 (17.7 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 4: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	150 g
HPMC, 6 cps	39.9 g
Tween 80 (polysorbate 80)	3 g
Purified water	801.3 g

Weight percent of dry content in suspension: 19.4 (10 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 5: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	150 g
HPMC, 6 cps	7.9 g
Purified water	449.4 g

Weight percent of dry content in suspension: 26 (12 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 6: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	60 g
Purified water	201 g

Weight percent of dry content in suspension: 23 (9.8 vol%).

Preparation of slurry and particles was done as in the example 1. The particles prepared were too fragile for handling.

Example 7: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	60 g
Purified water	440 g

Weight percent of dry content in suspension: 12 (4.7 vol%).

Preparation of slurry and particles was done as in the example 1. The particles prepared were too fragile for handling.

Example 8: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	183.7 g

Tween 80 (polysorbate 80)	4 g
Purified water	300 g

Weight percent of dry content in suspension: 38.5 (19.1 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.5 bar. The particles were fragile.

Example 9: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	100 g
HPMC, 6 cps	1.5 g
Tween 80 (polysorbate 80)	2 g
Purified water	155.3 g

Weight percent of dry content in suspension: 40 (20.3 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.25 bar. The particles were fragile.

Example10: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	100 g
HPMC, 6 cps	3.0 g
Tween 80 (polysorbate 80)	2 g
Purified water	157.5 g

Weight percent of dry content in suspension: 40 (20.6 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.25 bar. The particles were fragile.

Table
Characterization of microparticles

Example no	Dry content (wt%)	Dry content (vol %)	Binder (wt%)	Mercury porosity measurements		Mechanical strength	
				Bulk density	Pore median size (μm) (measured range: 0.0005-10μm)	kPa	Fraction
1	34	19.2	21	0.47	0.8	94	450-630 μm
3	31.8	17.7	21	0.48	0.7	125	300-400 μm
4	19.4	10	21	0.23	1.8	62	300-400 μm
5	26	12	5	0.35	1.6	25	300-400 μm
6	23	9.8	0	Not measured		Too fragile for handling	
7	12	4.7	0	Not measured		Too fragile for handling	
8	38.5	19.1	0	Not measured		Fragile, not coatable	
9	40	20.3	1.5	Not measured		Fragile, not coatable	
10	40	20.6	3	Not measured		Fragile, not coatable	

Of these examples, the particles from Examples 1 and 3 were tested and showed to endure the fluidisation in the fluid bed coating process.

9. As can be seen from the Table, the properties of the microparticles are a function of the relationship between the minimum dry content and the polymer binder content. The particles of Examples 1 and 3 possess the mechanical properties to be successfully coated by a fluidized bed coating process. The particles of Examples 4-10, wherein the minimum dry content is less than 15% by volume and/or the polymer binder content is less than 5%, are either too fragile for handling or do not possess the threshold mechanical properties to be coated by a fluidized bed coating process.

10. The comparative data shows that a better result is achieved with the claimed invention. Specifically, the microparticles prepared in accordance with Examples 1 and 3 have superior mechanical strength in comparison to the pellets of Examples 6-8 which, similar to Example 2 of Ratwatte, were prepared from a mixture without polymer, i.e., a binder.

Conclusion

Advantageously, the homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance. It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder. In accordance with the claimed invention, therefore, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. The claimed microparticles having a low friability can withstand coating with a polymeric film.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 7th October 2003

Anne Mari Juppo